

WORLD JOURNAL OF PHARMACEUTICAL RESEARCH

SJIF Impact Factor 7.523

Volume 6, Issue 13, 917-933.

Research Article

ISSN 2277-7105

ARTICAINE INFILTRATION- A SUBSTITUTE FOR CLASSICAL INFERIOR ALVEOLAR NERVE BLOCK IN LOWER MOLAR EXTRACTIONS: PROSPECTIVE CLINICAL STUDY.

Tripthi P. Shetty¹*, Ashish J. Rai², Prakyath Malli³, Padmaraj Hegde⁴ and Arvind Karikal⁵

¹Senior Lecturer, Dept. of Oral & Maxillofacial Surgery A B Shetty Memorial Institute of Dental Sciences, NITTE University, Mangalore.

²Senior Lecturer, Dept. of Oral & Maxillofacial Surgery A B Shetty Memorial Institute of Dental Sciences.

³Senior Lecturer, Dept. of Prosthodontics, Yenepoya Dental College, Yenepoya University, Mangalore.

^{4,5}Reader, Dept. of Oral & Maxillofacial Surgery A B Shetty Memorial Institute of Dental Sciences, NITTE University, Mangalore.

Article Received on 30 August 2017, Revised on 20 Sep. 2017, Accepted on 10 October 2017 DOI: 10.20959/wjpr201713-9897

*Corresponding Author Dr. Tripthi P. Shetty

Senior Lecturer, Dept. of
Oral & Maxillofacial
Surgery A B Shetty
Memorial Institute of Dental
Sciences, NITTE
University, Mangalore.

ABSTRACT

Objectives. The aim of this prospective study was to determine if Articaine local infiltrations adjacent to the lower molars requiring routine extraction can provide ample anesthesia thereby completely eliminating the need for classical inferior alveolar nerve block for the same. Study design. A hundred and eighty nine patients undergoing routine mandibular molar extractions were included in the study. Local infiltration around the tooth to be extracted was administered with 2ml 4% articaine hychloride with 1:100000epinephrine. The infiltration was deposited 1ml respectively on the buccal and lingual sides of tooth. The patients' compliance, comfort and level of anestesia was assessed by the subjective and objective signs. Results. Of the hundred and eighty nine patients included in the study between May 2017-

September 2017 87 patients were women (46%) and 102 men (54%) with a mean age of 43.42 years. Only articaine infiltration was sufficient to provide ample anesthesia for extraction in 79.89% of the patients. Lidocaine block was necessary in 3.70% of the cases. *Conclusions.* Articaine infiltrations prove to be an easy safe and relatively hassle free method

to produce ample anesthesia for simple mandibular molar extractions. Hence infiltration using articaine with its present success rate can definitely be considered as a satisfactory alternative option to nerve block techniques.

KEYWORDS: Articaine infiltration, Third molar extraction, Lignocaine, Classical inferior alveolar nerve block technique.

INTRODUCTION

Providing profound anesthesia to the patients during invasive dental procedure not only puts the patient at ease but also ensures a smooth sailing procedure; the outcome being superlative patient and surgeon satisfaction. Local anesthesia forms the back bone of pain control in dentistry and the hunt for a better anesthetic agent than the previous is never ending. Local anesthetics are the most commonly used injectable drugs in dentistry to reversibly block nerve conduction. The era of local anesthetics started with discovery of Cocaine in 1860. Later, the developments of Novocain 1904 and then Lignocaine by Lofgren and Lundquist in 1942 revolutionized dental practice. This soon became a gold standard drug against which all other new local anesthetics were compared to. [2]

In 1969, Articaine was synthesized by the chemist Muschaweck and was approved in 1975 as a local anesthetic in Germany. Articaine differs from the previous amide local anesthetics in that it has a thiophene ring in its molecule instead of the usual benzene ring. It was first named Carticaine, but its generic name was changed to Articaine in 1984.^[3]

Articaine is an amide local anesthetic with high lipid solubility due to the thiophene ring it contains. It also contains an ester group. The pharmacological characteristics of this anesthetic are responsible for its main advantages. Substitution of the aromatic ring with a thiophenic ring increased the liposolubility of the drug along with its potency (1.5 times greater than that of lidocaine). Moreover, articaine is the only amide local anesthetic containing an ester group in its molecular structure—thus allowing metabolization of the drug both by plasma esterases and by liver microsomal enzymes. The clinical advantages of Articaine include the duration of its an esthetic effect—only surpassed by ultra long acting anesthetics such as Bupivacaine, Etidocaine and Ropivacaine—and its superior diffusion through bony tissue. Articaine is claimed to be superior to lidocaine owing to its better diffusion through soft tissue and bone, the rapid onset, the excellent quality of the anaesthesia and the lower degree of toxicity. The contains the pharmacological characteristics of this anesthetics of the anaesthesia and the lower degree of toxicity.

Although related to permanent paraesthesia, articaine has been shown that it is safe and a very effective local anesthetic. The drug started to gain respect for its effectiveness in infiltration for management of pulpitis in mandibular teeth where the failure rate with inferior alveolar nerve block ranges from 44 to 81%. The success rate of obtaining anesthesia by buccal infiltration of mandibular first molar by articaine ranged in the literature from 54 to 94%. Although lidocaine inferior alveolar nerve block is a common dental injection in case of managing mandibular teeth, it may not be the first choice in specific situations where in the procedure of the nerve block injection it-self is contraindicated. [4,7]

The classical inferior alveolar nerve (IAN) block technique although is the mainstay to provide anesthesia for extraction of lower molar teeth it is however technique sensitive requiring at least the minimal knowledge of bony and soft tissue anatomic land marks. It also requires adequate mouth opening of the patient for visibility and accessibility. Also, to provide complete anesthesia to the molars being extracted IAN block needs to be supplemented with long buccal and lingual nerve blocks.

Our study therefore aims in deducing if only articaine local infiltrations around the mandibular molar teeth indicated for extraction would suffice to provide profound anesthesia where in the extraction procedure can be carried out devoid of any need for the routine IAN block.

MATERIALS AND METHODS

One hundred and eighty nine patients visiting the department of oral and maxillofacial surgery at A.B.S.M.I Dental Sciences and Hospital requiring routine extractions of mandibular molar teeth in were included in the study. The study spanned May 2017-September 2017. Included in the study were women and men with a mean age of years.

Criteria for inclusion of patients

- a) Patient willing to give informed consent
- b) Patients of both sexes.
- c) Patients between 25 60 years of age.
- d) Patient indicated for routine mandibular molar extractions.

Criteria for exclusion of patients

- a) The presence of uncontrolled diabetes, immune disease, or other contraindicating systemic conditions
- b) Radiation therapy to the head and neck region in the 12 months before the proposed therapy
- c) Chemotherapy in the 12-month period earlier the proposed therapy.
- d) Pregnant patients

MATERIALS

2 ml of 4% ArticaineHCl with 1: 100000adrenaline.

Hypodermic needles

Dental syringe for cartridges

2% Lignocaine HCl with 1: 100000adrenaline.

Disposable syringe with 1.5 inch, 26 gauge needle.

Standard extraction instruments [Figure 1,2]

METHOD

A total of hundred and eighty nine patients satisfying the above criteria requiring routine extraction of mandibular molars were selected for the study. Local infiltration around the tooth to be extracted was administered with 2ml 4% articaine hychloride with 1:100000epinephrine. The infiltration was deposited 1ml respectively on the buccal and lingual sides of tooth. The patients' compliance, comfort and level of anestesia were assessed by the subjective and objective signs. If the patients had the desired subjective and objective signs within first 6 minutes after infiltration, extraction was performed. If the anesthetic effect was not satisfactory as per the operator's satisfaction a second dosage of 2ml 4% articaine hychloride with 1:100000 epinephrine was repeated as above on either side of tooth, 1ml each. The subjective and objective signs were assessed again in the next 5 minutes and if satisfactory, extraction was done. Failure to achieve adequate anesthesia even with 2 doses of Articaine infiltration called for the classic inferior alveolar nerve block with 2% lidocaine with 1:100000epinephrine to be administered. [Figure 3].

All of the one hundred and eightynine patients were injected with the articaine infiltration and the Lignocaine IAN block if necessary by the same operating surgeon. They were all assessed for the level of anesthesia as per the numeric pain scale by another examiner blinded to the study.

STATISTICAL ANALYSIS

The 189 patients included in the study were grouped under 4categories depending on the diagnosis for which the tooth was indicated for extraction. They included extraction due to

- Carious / Decayed teeth
- Pulpal Involvment / Pathology
- Infection / Abscess
- Others (Fractured teeth, supernumerary teeth)

The parameters assessed were:

- The level of anesthesia in the first 6 minutes following local infiltration with articaine (Pain Analogue Scale)
- Number of patients requiring a second dose of above mentioned infiltration
- Number of patients requiring IAN block with lignocaine for pain control
- Number of patients in whom both the methods of anethesia failed.

The assessment was done using the numeric pain scale correlating it with the level of anesthesia.

Within each group, the above mentioned parameters were assessed individually.

RESULTS

The study included a total of 189 cases, 87 female patients (46%) and 102 male patients (54%)[**Table 1**] requiring routine extraction of lower molars [**Table 2**]. Depending on the indicated lower molar tooth of extraction, they were subcategorised into carious / decayed teeth (n=119; 62.96%), pulpally involved/associated with pathology (n=38; 20.11%), infected / abscess (n=22; 11.64%), others (fractured teeth, supernumerary teeth: n=10; 5.29%).[**Table 3**, **Graph 1**].

Overall of the 189 cases, 151 (79.89%) of them had profound anesthesia as implied on the pain scale indicating the efficacy of articaine infiltration in less than 3 minutes. 15 cases (7.93%) showed profound anesthesia during 3 to 6 minutes after local infiltration. 13 (6.87%) cases were more comfortable undergoing the extraction after the second dose of the same articaine infiltration. Anesthesia even after second infiltration was not adequate enough and hence lignocaine block was administered in 7 cases (11.64%). Both local infiltration and nerve block seemed to have failed in 3 cases (5.31%). [Table 4].

In the decayed category (n=119), 103 cases (86.55%) underwent extraction post a single dose of anesthesia effective in less than 3 minutes. 6 cases (5.05%) showed a delayed onset of profound anesthesia between 3 to 6 minutes. A second dose of articaine local infiltration for comfortable extraction was required in 7 cases (5.88%). 3 cases (2.52%) required lidocaine nerve block and no failure was seen overall in this category.[**Table 5, Graph 2**].

Similarly the pulpal involved/ pathology category (n=38) was assessed similarly. 31 cases (81.57%) underwent extraction post a single dose of anesthesia effective in less than 3 minutes and 4 cases (10.54%) showed delayed onset of profound anesthesia between 3 to 6 minutes. A second dose of articaine local infiltration for comfortable extraction was required in 1 case (2.63%). 2 cases (5.26%) required lidocaine nerve block and no failure was seen overall in this category. [Table 6, Graph 3].

Assessment of the infection category (n=22) showed 15 cases (68.18%) comfortably undergoing extraction post a single dose of anesthesia effective in less than 3 minutes and 3 cases (13.63%) showed delayed onset of profound anesthesia between 3 to 6 minutes. A second dose of articaine local infiltration for comfortable extraction was required in 1 case (4.54%). The need for lidocaine nerve block was comparatively higher in this group; 2 cases (9.09%). Failures of both blocks were seen in 1 case (4.54%). [Table 7, Graph 4].

The last category (n=10) had 2 cases (20%) each in both less than 3 minutes and the 3 to 6 minutes group. A second dose of articaine local infiltration was required in 4 cases (40%). 2 cases (20%) showed failure in both techniques of anesthsia. [Table 8, Graph 5].

As a whole, off the 189 cases, 179 (94.70%) of them underwent routine extraction of lower molar teeth with just articaine local infiltration as the asnesthetic cover either in single or double dose. This only goes to show that articaine infiltration as profound anesthesia as any other nerve block technique.

Table 1: Demographic characteristics of the study population.

Variables	n=189
Age	
Mean S.D.	43.42 ± 9.85
Gender	
Male	102 (54.0%)
Female	87 (46.0%)

922

Table 2: Details of extracted tooth.

Tooth Number	N	%
36.00	49	25.9
37.00	29	15.3
38.00	7	3.7
46.00	71	37.6
47.00	25	13.2
48.00	8	4.2

Table 3: Reason behind extraction of tooth.

Tooth Number	N	%
Decayed	119	62.96
Pulp Involvement	38	20.11
Infection	22	11.64
Other	10	5.29

Table 4: Pain analogue scale in correlation with anesthesia.

	No Pain (profound Anaesthesia Effective < 3 minutes) 0	Mild Pain(Ample anaesthesia in 3-6 minutes) 1	Moderate Pain(need for second infiltration)	Severe Pain(need for lidocaine nerve block) 3	Unbearable pain (failure of block as well) 4
No. Of Patients	152	15	13	7	2
%	79.89%	7.93%	6.87%	3.70%	1.58%

Table 5: Decay category (n=119).

	Effective < 3 min	3-6min	Second dose infiltration	Lidocaine block	Failure
n	103	6	7	3	-
percentage	86.55%	5.04%	5.88%	2.52%	

Table 6: Pulp involvement category (n=38).

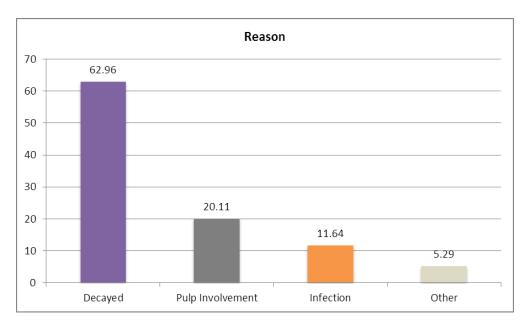
	Effective < 3 min	3-6min	Second dose infiltration	Lidocaine block	Failure
n	31	4	1	2	-
percentage	81.57%	10.52%	2.63%	5.26%	

Table 7: Infection category (n=22).

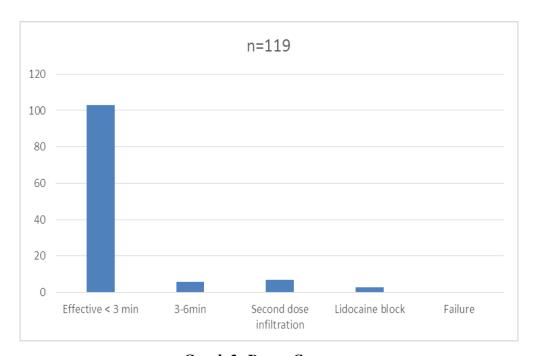
	Effective < 3 min	3-6min	Second dose infiltration	Lidocaine block	Failure
n	15	3	1	2	1
percentage	68.18%	13.63%	4.54%	9.09%	4.54%

Table 8: Others (n=10).

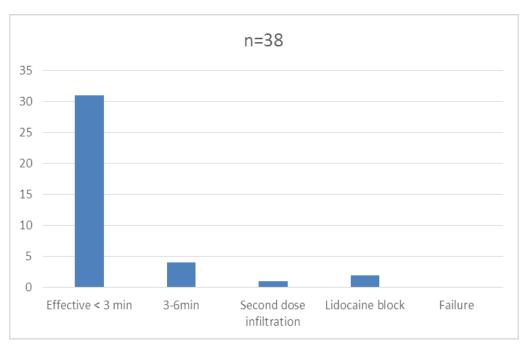
	Effective < 3 min	3-6min	Second dose infiltration	Lidocaine block	Failure
n	2	2	4		2
percentage	20%	20%	40%		20%



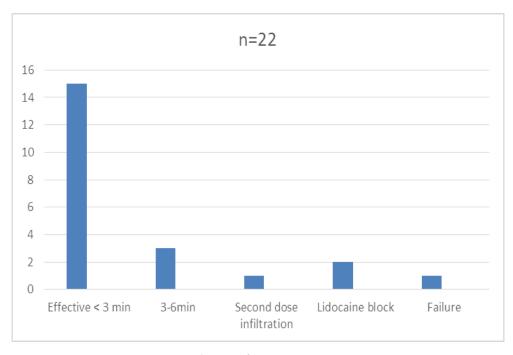
Graph 1: Reason behind extraction of tooth.



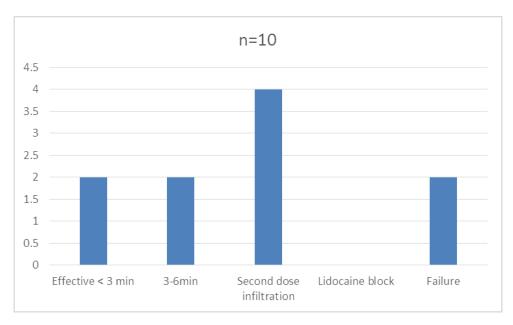
Graph 2: Decay Category.



Graph 3: Pulp involvement category.



Graph 4: Infection category.



Graph 5: Others.



FIGURE 1: Materials.



FIGURE 2: Dental syringe loaded with Articaine Cartridge.



FIGURE 3: Local infiltration administration.

DISCUSSION

Pain itself is multifactorial; perception and pain reaction varies greatly among individuals.^[4] Local anesthetics, the indispensible arsenal of dentistry blocks the sensation of pain by interfering with the propagation of peripheral nerve impulses. Both the generation and the conduction of action potentials are inhibited. Electrophysiological data indicate that local anesthetics do not significantly alter the normal resting potential of the nerve membrane; instead, they impair certain dynamic responses to nerve stimulation (Strichartz & Ritchie 1987). Local anesthetics interfere with nerve conduction by blocking the influence of stimulation on Na+ permeability.^[2] For the efficacy of local anaesthesia multiple variable factors exist like technique variability, anatomic variations, complexity of procedure and reporting error.^[4]

The first substance that was used for this purpose was cocaine, as far back as in 1884. In 1903, Braun suggested using adrenaline as a "chemical tourniquet" to prolong the duration of local anesthetics. In 1904 Einhorn synthesized procaine, an ether anesthesia. In the 1940's a new group of local anesthetic compounds, the amides, were introduced. The initial amide local anesthetic, lidocaine, was synthesized by the Swede chemist Nils Løfgren in 1943. Lidocaine revolutionized pain control in dentistry worldwide, as it was both more potent and less allergenic than procaine. The discovery of Lidocaine has been landmark in the history of local anesthetic. Today it is considered as a reference standard against which other local anesthetic agents are compared. [2]

Articaine hydrochloride (HCl) in 1969 with the name of Carticaine, was first marketed in Germany in 1976. The pharmacological characteristics of this anesthetic are responsible for

its main advantages. It differed from the previous amide local anesthetics in that it was derived from thiophene and because of that contained a thiophene ring in its molecule instead of the usual benzene ring. Though first named Carticaine, its generic name was changed to articaine in 1984 and was introduced onto the German market in 1969.^[6]

The articaine solution's plasma half-life has been reported to be as short as 20 minutes versus^[5] lidocaine's half-life of approximately 108 minutes in healthy patients.^[7] Adverse reactions to articaine are characteristic of those associated with other amide-type anesthetics. 8 For a healthy adult weighing 70 kilograms, the maximum dose for a local anesthetic solution equates to seven carpules (1.7 milliliters) of 4 percent articaine or 13 carpules (1.8 mL each) of 2 percent lidocaine.^[8]

Articaine is an amide derivative with a "thiophene ring" in its molecular structure instead of usual benzene ring, making it more lipophilic thus accounting for its diffusion properties within tissues and bones resulting in faster onset of action compared with lignocaine.^[4] This is the reason profound anaesthesia was achieved only with infiltration of 4% Articaine in 94.70% cases in this study.

In comparison with other amide-type local anaesthetics, articaine contains a carboxylic ester group. Thus, Articaine is inactivated in the liver as well as by hydrolization in the tissue and the blood. Articaine is the only local anesthetic agent, which is inactivated in both ways. Since the hydrolization is very fast and starts immediately after injection, about 85 to 90% of administered articaine is inactivated in this way. Main metabolic product is arti-cainic acid (or more accurately: articainic carboxylic acid), which is nontoxic and inactive as local anesthetic. When Articaine is injected, the concentration of active drug at the site of injection is nearly twice that obtained when Lignocaine is used. [4] Hence local infiltration was able to produce similar anaesthesia as nerve block in 179 off the 189cases.

Keeping the efficacy in mind, articaine is a safer local anesthetic agent similar to other group of local anesthetic agents. A study was carried out to examine an interaction of lidocaine, articaine and mepivacaine with some antihypertensive drugs clonidine and reserpine on the pentylenetetrazole induced seizures and the conclusion drawn was articaine is one of the safest local anesthetic and can be used in epileptic patients.^[4]

The inferior alveolar nerve block is the most commonly used injection technique to anesthetize lower teeth. [9,15] The nerve block techniques have their own drawbacks namely.

- Accuracy in identifying the landmarks both hard and soft tissue
- Ample mouth opening mandatory for accessibility and visibility to administer the block
- Multiple pricks i.e. supplemental injection of long buccal and lingual nerve book
- Can cause complications oh haematoma, trismus, IAN injury to name a few.
- Failure rates of IAN block are higher (15-20%). [9]

The present study compared the efficacy of 4% articaine (1:100,000 adrenaline) to produce anesthesia profound enough to perform routine simple extraction of mandibular molar teeth. The potency of articaine in infiltration was reported in anesthetizing maxillary teeth with single buccal infiltration without the need for palatal anesthesia as the drug was able to penetrate the bone effectively and reach the other side. [1] This study head started the idea for our present study.

Articaine is a widely used local anesthetic which has been proved to be as effective as lidocaine and has longer duration of action. Buccal infiltration of articaine has been shown to be effective in anesthetizing mandibular first molars teeth. It was also reported that articaine is more effective in infiltration than lidocaine. In our study articaine infiltration was found to be relatively more effective in decayed teeth (86.55%) as compared to tooth associated with periapical infection (68.18%) and fractured teeth (20%). The high failure rates in the last two groups 4.54% and 20% respectively can be attributed to the fact that although diffusibility to bone remains unchanged, the ability to produce pulpal anesthesia reduces owing to a large number of associated factors.

When one cartridge was not enough to obtain profound local anesthesia another cartridge was used effectively in some cases in the present study. This is not considered a real failure as the maximum dose of 4% articaine is 7.0 mg/kg which is equal to a total of 7 cartridges for adult healthy patients.^[19] But in this current study we considered it as indication to induce anesthesia with nerve block using lignocaine.

CONCLUSION

Clinically significant advantage of articaine better haemostatic and bone diffusibility. [2] Articaine is proved to an excellent alternative to lignocaine. [3] Reports of toxicity reactions are extremely rare when articaine is used. Rapid inactivation of plasma esterases may explain

the apparent lack of overdose reactions even though it is marketed as 4%.^[7] Clinical advantages like a shorter time of onset, longer duration of action and greater diffusing property over lignocaine could be proved.^[3]

The present study had a very simple but important aim. Are articaine local infiltrations enough to produce ample anesthesia to perform routine mandibular molar extractions thereby eliminating the need for nerve blocks. Through our study we can state safely that infiltration using articaine with its present success rate using one cartridge can definitely be considered as a satisfactory alternative option to nerve block techniques. In the present study surgeons were satisfied with efficacy articaine infiltration. The same results were found in patient's satisfaction and pain visual analogue scores.

Articaine infiltrations hence proved to be an easy safe and relatively hassle free alternative to IAN nerve block with lidocaine in simple mandibular molar extractions. It is however not very effective in extraction of lower molar teeth indicated for extraction due to infection and tooth fractures owing improper diffusion. Further studies however on a larger group of population are recommended for greater authenticity of this relatively new and unpopular drug in oral and maxillofacial surgery in India.

REFERENCES

- 1. Walid Ahmed Abdullah, Hesham Khalil, Saad Sheta. Articaine (4%) buccal infiltration versus lidocaine (2%) inferior alveolar nerve block for mandibular teeth extraction in patients on warfarin treatment. J Anesth Clin Res., 2014; 5(8): 1000434.
- 2. Deepashri H. Kambalimath, R. S. Dolas, H. V. Kambalimath, S. M. Agrawal. Efficacy of 4% articaine and 2% lidocaine: A clinical study. J. Maxillofac. Oral Surg., 2013; 12(1): 3–10.
- 3. Ryan G. Brandt, Patricia F. Anderson, J. McDonald, Woosung Sohn, Mathilde C. Peters. The pulpal anesthetic efficacy of articaine versus lidocaine in dentistry: A meta-analysis. JADA, 2011; 142(5): 493-504.
- 4. Shahid Hassan, Ajaz Shah, Manzoor Dar, Tajamul Hakeem, Zahoor Teli. Comparison of articaine and lidocaine used as dentalocal anesthetics-a research article. IOSR-JDMS. 2015; 14(8): 123-128.
- 5. Rahn R, Ball B. Local Anesthesia in Dentistry -Articaine and Epinephrine for Dental Anesthesia. 1st ed. Seefeld (Germany): 3M ESPE AG; 2001.

- 6. Malamed SF, Gagnon S, Leblanc D. Articaine hydrochloride- the study of safety of a new amide local anesthetic. J Am Dent Assc. 2001; 132: 177-185.
- 7. Malamed SF, Gagnon S, Leblanc D: A comparison between articaine HCL and lidocaine HCL in pediatric dental patients. Pediatric dentistry, 2000; 22: 4: 307-11.
- 8. Vree TB, Gielen MJM: Clinical pharmacology and the use of articaine for local and regional anaesthesia. Best Practice& Research Clinical Anaesthesiology, 2005; 19: 2: 293-308.
- 9. Claffey E, Reader A, Nusstein J, Beck M, Weaver J. Anesthetic efficacy of articaine for inferior alveolar nerve blocks in patients with irreversible pulpitis. J Endod. 2004; 30: 8: 568-71.
- 10. Zolkowska D, Pikula A, Borzecki A, Sieklucka-Dziuba M. Interaction between local anesthetics and centrally acting antihypertensive drugs. Ann Univ Mariae Curie Sklodowska [Med]. 2002; 57(1): 569-73.
- 11. Hawkins J M, Moore PA. Local Anesthesia: Advances in agents and techniques. Dent Clin N Am, 2002; 46: 719-732.
- 12. Robertson D, Nusstein J, Reader A, Beck M, McCartney M. The anesthetic efficacy of articaine in buccal infiltration of mandibular posterior teeth. JADA, 2007; 138(8): 1104-1112.
- 13. Claffey E, Reader A, Nusstein J, Beck M, Weaver J. Anesthetic efficacy of articaine for inferior alveolar nerve blocks in patients with irreversible pulpitis. J Endod, 2004; 30(8): 568-571.
- 14. Mikesell P, Nusstein J, Reader A, Beck M, Weaver J. A comparison of articaine and lidocaine for inferior alveolar nerve blocks. J Endod, 2005; 31(4): 265-270.
- 15. Donaldson D, James-Perdok L, Craig BJ, Derkson GD, Richardson AS. A comparison of Ultracaine DS (articaine HCl) and Citanest forte (prilocaine HCl) in maxillary infiltration and mandibular nerve block. J Can Dent Assoc, 1987; 53(1): 38-42.
- 16. Oertel R, Rahn R, Kirch W. Clinical pharmacokinetics of articaine. Clin Pharmacokinet, 1997; 33(6): 417-425.
- 17. Vree TB, Baars AM, van Oss GE, Booij LH. High-performance liquid chromatography and preliminary pharmacokinetics of articaine and its 2-carboxy metabolite in human serum and urine. J Chromatogr, 1988; 424(2): 440-444.
- 18. Thomson PD, Melmon KL, Richardson JA, et al. Lidocaine pharmacokinetics in advanced heart failure, liver disease and renal failure in humans. Ann Intern Med, 1973; 78(4): 499–508.

- 19. Malamed SF, Gagnon S, Leblanc D. Articaine hydrochloride: a study of the safety of a new amide local anesthetic. JADA, 2001; 132(2): 177-185.
- 20. Pogrel MA. Permanent nerve damage from inferior alveolar nerve blocks: an update to include articaine. J Calif Dent Assoc, 2007; 35(4): 271-273.
- 21. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ, 1996; 312(7023): 71-72.
- 22. Carr AB. Systematic reviews of the literature: the overview and meta-analysis. Dent Clin North Am, 2002; 46(1): 79-86.
- 23. Needleman IG. A guide to systematic reviews. J Clin Periodontol, 2002; 29(suppl 3): 6-9.
- 24. Katyal V. The efficacy and safety of articaine versus lignocaine in dental treatments: a meta-analysis (published online ahead print Dec. 16, 2009). J Dent, 2010; 38(4): 307-317. doi:10.1016/j.jdent. 2009.12.003
- 25. Ram D, Peretz B. Administering local anaesthesia to paediatric dental patients: current status and prospects for the future. Int J Paediatr Dent, 2002; 12(2): 80-89.
- 26. Malamed SF, Gagnon S, Leblanc D. A comparison between articaine HCl and lidocaine HCl in pediatric dental patients. Pediatr Dent, 2000; 22(4): 307-311.
- 27. Sierra Rebolledo A, Delgado Molina E, Berini Aytís L, GayEscoda C. Comparative study of the anesthetic efficacy of 4 percent articaine versus 2 percent lidocaine in inferior alveolar nerve block during surgical extraction of impacted lower third molars. Med Oral Patol Oral Cir Bucal, 2007; 12(2): e139-e144.
- 28. Maniglia-Ferreira C, Almeida-Gomes F, Carvalho-Sousa B, et al. Clinical evaluation of the use of three anesthetics in endodontics. Acta Odontol Latinoam, 2009; 22(1): 21-26.
- 29. Matthews R, Drum M, Reader A, Nusstein J, Beck M. Articaine for supplemental buccal mandibular infiltration anesthesia in patients with irreversible pulpitis when the inferior alveolar nerve block fails. J Endod, 2009; 35(3): 343-346.
- 30. Anisimova EN, Zorian EV, Shuga lov IA. The characteristics of the action of Carpule-delivered local anesthetics and their combinations with vasoconstrictors (a preliminary report) (in Russian). Stomatologiia (Mosk), 1997; 76(6): 25-29.
- 31. Amsel V, Katanec D. Comparison of the effect the local anesthetics xylocaine and cystocaine in oral medicine (in Croatian). Acta Stomatol Croat, 1986; 20(3): 199-206.
- 32. Sitzmann F, Lindorf HH. Comparative experimental measurement of the stimulus threshold of the effect of the local anesthetic Ultracaine (Carticaine) (in German). Dtsch Zahnarztl Z, 1976; 31(2): 128-130.

- 33. Khoury F, Hinterthan A, Schürmann J, Arns H. Clinical comparative study of local anesthetics: random double-blind study with four commercial preparations (in German). Dtsch Zahnarztl Z, 1991; 46(12): 822-824.
- 34. Szabó G, Gáspár L, Divinyi T. Recent clinical experiences with Ultracaine preparations versus different lidocaines (in German). Z Stomatol, 1988; 85(4): 235-238.
- 35. Mehta Fali S, Daftary Dinesh K, Billimoria RB, Irani RR. Carticaine in dentistry. J Indian Dent Assoc, 1983; 55(12): 501-505.
- 36. Corbett IP, Kanaa MD, Whitworth JM, Meechan JG. Articaine infiltration for anesthesia of mandibular first molars. J Endod, 2008; 34(5): 514-518.
- 37. Wahl MJ, Schmitt MM, Overton DA. Injection pain of prilocaine plain, mepivacaine plain, articaine with epinephrine and lidocaine with epinephrine. Gen Dent, 2006; 54(3): 168-171.
- 38. Nusstein J, Burns Y, Reader A, Beck M, Weaver J. Injection pain and post injection pain of the palatal-anterior superior alveolar injection, administered with the Wand Plus system, comparing 2 percent lidocaine with 1:100,000 epinephrine to 3 percent mepivacaine. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2004; 97(2): 164-172.
- 39. Elad S, Admon D, Kedmi M, et al. The cardiovascular effect of local anesthesia with articaine plus 1:200,000 adrenalin versus lidocaine plus 1:100,000 adrenaline in medically compromised cardiac patients: a prospective, randomized, double blinded study. Oral Sur Oral Med Oral Pathol Oral Radiol Endod, 2008; 105(6): 725-730.